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Cognition-Enhancing Drugs and Their Appropriateness for Aviation and Ground Troops: A Meta-Analysis

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14. ABSTRACT

Currently, there are a number of pharmaceuticals available that have potential to enhance cognitive functioning which will inevitably be considered for use in military operations for enhancement purposes. Some drugs such as modafinil and caffeine have already been tested for use in military operations and some drugs used for cognition enhancement are already included in Army policy in terms of their approved use. There is considerable research available on these drugs. However, military policy regarding use must be based on high-quality research studies. The goal of this study was to review the literature and conduct a meta-analysis to determine quality of the research available and to synthesize the current state of knowledge of these potentially cognition enhancing drugs. A meta-analysis of the 3 studies that met all inclusion criteria revealed a relatively weak pooled effect of modafinil on some aspects of cognitive performance in normal, rested adults. While the results of this study support the efficacy of modafinil, the main finding is the large literature gap evaluating the short and long term effects of these drugs in healthy adults.

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Introduction

The U.S. military is constantly striving for optimal physical and mental performance from its warfighters. One strategy to improve cognitive performance that is inevitably discussed involves the use of pharmaceuticals. Currently, there are a number of pharmaceuticals available that have potential to enhance cognitive functioning. Available drugs include, but are not limited to, beta-blockers, typically prescribed for cardiac arrhythmia; methylphenidate, prescribed attention-deficit disorder (ADD); modafinil, a wake-promoting agent for those with sleep disorders; and an acetylcholinesterase inhibitor, donepezil, typically prescribed for those with Alzheimer's disease (AD). All of these medications are prescribed for therapeutic effect not related to cognition enhancement. Caffeine, on the other hand, is available without a prescription, and is frequently used specifically for its stimulant properties which impact attention. Pharmaceutical companies are also researching more substances to be used as "smart drugs" which could arrive on the market over the next few years.

A number of ethical concerns are raised with regard to the use of these drugs as a means of enhancement and not for the intended therapeutic purpose (see Russo, 2007, for a detailed discussion). Despite these concerns, these drugs will inevitably be considered for use in military operations for enhancement purposes. Some drugs such as modafinil and caffeine have already been tested for use in military operations and some drugs used for cognition enhancement are already included in Army policy in terms of their approved use. There is considerable research on these drugs and their approved uses. A review of current literature suggested that there was surprisingly little information available regarding specific cognition-enhancing properties of these frequently-discussed drugs. Cognition efforts in normal healthy individuals are central to the performance-enhancing properties of any drug considered for operational use. The goal of this study was to review the literature and conduct a meta-analysis to determine what is currently known about the effect of these drugs on cognitive performance under normal and operational stress conditions. The results of this study have implications for future experimental research on the effects of cognition enhancing drugs on performance in military operations as well as the immediate suitability of these agents for use by aviators and ground troops.

Military significance

Soldiers must perform under conditions of stress including fatigue, thermal extremes, altitude, and nutritional deprivation. The U.S. Army is continuously working to determine techniques and countermeasures to sustain performance under these conditions. Considerable amounts of research has shown that these stressors decrement both cognitive and physical performance. Both pharmacologic and non-pharmacologic interventions have been identified and approved for use in operations to diminish these negative effects. However, this is a continuous effort and pharmacologic interventions to sustain and enhance cognitive performance may be applicable for these purposes in both aviation and ground troops.

Background

The use of cognition enhancement drugs has attracted much attention over recent years. The topic has appeared in widely distributed newspapers such as the *New York Times* (e.g., Carey,

2008). In April of 2008, the journal *Nature* published results of an informal survey polling readers regarding use of three specific cognition enhancement agents (Maher, 2008). The results indicated that approximately 20% of the respondents reported use of the agents for non-therapeutic enhancement purposes. The majority of the respondents (69%) agreed that healthy adults should have the option to use cognition enhancement agents. To what population these results generalize is limited given that the informal survey (poll) is subject to biases (e.g., selection bias). The survey results do suggest, however, that use of pharmaceuticals for cognition enhancement purposes is becoming increasingly popular and socially accepted; good scientific research is needed to fully analyze the costs and benefits.

The effectiveness of cognition enhancement pharmaceuticals is variable and dependent on factors such as baseline performance and dosage. For example, some drugs are shown to enhance performance for those that perform at a "low" baseline level and do not enhance or may even hinder performance for those that perform at a "high" baseline level. Also, an underdose or overdose may enhance or hinder performance (see de Jongh, Bolt, Schermer, and Olivier, 2008 for a review).

Many of the currently available substances with potential to enhance cognitive performance are discussed in Army policies in terms of their approved use (e.g., Department of the Army, 2006). The use of these substances is highly regulated and restricted. A few of the potential cognition enhancement agents are discussed below (see Lanni et al., 2008, for a review).

Anti-anxiety drugs

Beta blockers, prescribed for many years for cardiac arrhythmia and high blood pressure, have been shown to reduce anxiety in connection with their effects on the sympathetic nervous system (i.e., β-adrenergic antagonist). They have a reputation for reducing social and performance anxiety which, in turn, may improve cognitive performance. They are readily recognized by their generic names ending in "-olol" (Note: the exception is labet<u>a</u>lol, which also has α_1-blocking properties). There is evidence of their ability to improve shooting accuracy (Kruse, et al., 1986); however this effect may be due to reduced hand tremor. In addition, the beta blocker propanolol has been shown to prevent the consolidation of unwanted memories, an interesting aspect of performance enhancement. In general, the performance-enhancing effects of beta-blockers appear to be subtle, the side effects well-described and not insignificant, and they are not commonly advocated for operational use.

Attention enhancement drugs

Pharmaceuticals that enhance attention (e.g., methylphenidate) are becoming increasingly popular among students as study aids on college campuses across the country. Methylphenidate blocks the reuptake of dopamine and norepinephrine thus increasing synaptic concentration. It has been used extensively in treating ADD and narcolepsy. The effects of methylphenidate in healthy populations are promising; however, its potential for abuse is high, given its pharmacological similarity to cocaine (Bray, et al., 2004).

Wake agents

Modafinil is a wake agent typically used to treat sleep disorders. Its mechanism of action is unclear, but it is believed to act as an antagonist to the dopamine reuptake transporter (LeDuc, et al., 2009) and decrease GABA-mediated neurotransmission (Ferraro et al., 1996). Dextroamphetamine is a stimulant used to treat ADHD and sleep disorders such as narcolepsy. It is a dopamine agonist, and has been shown to increase wakefulness and alertness and enhance speed of simple mental tasks (Caldwell, Caldwell, and Crowley, 1997). At the time of this writing, US Army policy does not permit the use of modafinil for management of fatigue but does approve use of dextroamphetamine under carefully controlled circumstances. The U.S. Air Force, however, has approved the use of both modafinil and dextroamphetamine for aircrew fatigue management. Caffeine is a widely used stimulant available over the counter, even making its way into chewing gum and "energy" drinks. It increases vigilance and alertness by leading to increased cyclic adenosine monophosphate levels. Caffeine is approved by the U.S. Army as a fatigue countermeasure for short-term use (see Department of the Army, 2009, for detailed guidelines).

Memory enhancement drugs

Available pharmaceuticals that have been shown to enhance memory include acetylcholinesterase inhibitors (e.g., donepezil) which are typically used to treat AD. Preliminary studies showed that subjects given donepezil exhibited superior training retention (Yesavage et al., 2002). These results are controversial however due to study design limitations. Most studies recommend that participants take donepezil for at least 21 days to obtain an effect. Research has also shown donepezil can enhance rapid eye movement (REM) sleep (Schredl et al., 2006). More research is needed to examine whether REM sleep enhancement is related to improved memory performance.

Operational environment effects

For any performance-enhancing drug to be suitable for use in a military population (ground and/or aviation troops), the cognitive enhancement effects must hold up under conditions of operational stress. There are numerous battlefield stressors that negatively impact cognitive performance. Lieberman et al. (2005) found declining vigilance, learning, memory and reasoning in Soldiers undergoing a 53-hour field exercise with stressors like dehydration, sustained physical activity, and sleep deprivation. More detailed information regarding the effects of cognitive-enhancing drugs on specific operational stressors is presented below.

Effects of environmental stressors

The military environment features a variety of environmental extremes – temperature, altitude, hydration, etc. – that can affect a Soldier's response to pharmaceuticals. In 2006, 220 cases of heat stroke among U.S. Soldiers resulting in 57 hospitalizations were reported. These injuries occurred in both garrison and operational environments (Department of the Army, 2007). Dehydration in hot environments impairs both physical and mental performance and is a major cause of heat related illnesses. A review of the literature failed to find studies examining the

effects of cognitively enhancing drugs on environmental stressors like heat stress and dehydration. However, it is known that medications like beta-blockers often contribute to heat-related illness as they impair heat reduction mechanisms (Finnoff, 2008), and pharmaceuticals can be profoundly affected by hydration levels.

Glucose, the main source of energy in the brain, is rapidly exhausted during mental activity. Neurons depend on a constant supply of glucose (Zillmer and Spiers, 2001). In times of malnutrition, one's intake of carbohydrates in drastically reduced. Volkow et al., (2008) found that methylphenidate decreased the amount of glucose needed by the brain to perform numerical calculations in healthy adults. Also, some research claims that donepezil could have a beneficial effect on memory in patients with Wernicke-Korsakoff's syndrome which results from low thiamine and is typically associated with long-term alcohol abuse or malnutrition (Sahin, Gurvit, Bilgic, Hanagasi, and Emre, 2002).

Effects of sleep deprivation

Caffeine, dextroamphetamine, and modafinil have all been studied extensively and have been shown to restore and sustain cognitive performance during sleep deprivation (e.g., Wesensten, Killgore, and Balkin, 2005). Walsh, Randazzo, Stone, and Schweitzer (2004) examined the effects of 200 mg of modafinil during four consecutive simulated night shifts and found modafinil attenuated the effects of sleep deprivation in vigilance and executive function tasks compared to placebo. The U. S. Army Aeromedical Research Laboratory recently completed an assessment of 100 mg modafinil and 5 mg dextroamphetamine throughout 40 hours of continuous wakefulness (Estrada et al., n.d.). Results showed that the stimulants maintained alertness, cognitive function, judgment, and risk perception in sleep deprived aviators better than placebo without side effects of aeromedical concern.

While this cursory review of the literature suggests cognitive function may be affected by these agents, it is important to base pharmacological treatment of Soldier only on high quality research studies. To assess the quality of the available literature, a systematic and critical review of the available literature (e.g., a meta-analysis) was undertaken.

Research objectives

There were two objectives of the present study: 1) to conduct a meta-analysis to determine the positive and negative effects of cognition enhancement drugs in aviation and ground military operations, and 2) to identify gaps in the literature and areas for future research.

Methods

Literature search and study eligibility

Literature searches were conducted in mainstream databases, including Defense Technical Information Center (DTIC), PubMed/Medline, clinicaltrials.gov, and PsycInfo. The literature search included "gray" (difficult to locate) literature, which required the assistance of a

professional librarian on staff at the U.S. Army Aeromedical Research Laboratory. The keywords included in the search are displayed in table 1.

Table 1.
Keywords included in literature search.

Categories	**Keywords**
Drug Names	Modafinil
	Caffeine
	Donepezil
	Beta-blockers
	Dopamine agonists
	Methylphenidate
Cognitive Functions	Memory
	Attention
	Decision Making
	Judgments
	Cognition
	Enhancement
Operational Stress	Sleep Deprivation
	Fatigue
	Heat Stress
	Cold temperature
	Malnutrition
	Stress

Eligibility

The inclusion criteria were set to be conservative in order to increase homogeneity and ensure a high level of study quality. To be included in the meta-analysis, a study must have the following characteristics: a) randomly controlled trial (RCT) design, b) between-subjects design, c) healthy human subjects aged 18-50 years, d) assessments of cognition-enhancement using valid and reliable cognitive performance measures, and e) published in the English language. Study exclusion and inclusion criteria are provided in table 2.

Table 2.
Study inclusion and exclusion criteria.

Criteria	Included	Excluded
Study Designs	RCTs	All but RCT
Test Populations	Age: 18 to 50 years	Age: under 18 years and over 50 years
	Race: Any	Race: None
	Males and females	Gender: None
	Healthy	Unhealthy or abnormal
	Nationality: Any	Nationality: None
Interventions	Modafinil: all doses	All combination therapy
	Caffeine: all doses	Non-pharmacological treatment
	Donepezil: all doses	
	Beta-blockers: all doses	
	Dopamine agonists: all doses	
	Methylphenidate: all doses	
Language	English language	Non-English language
Comparisons	Experimental Group compared to Control Group	Within-subjects studies, case studies,
Outcome Measures	Valid and reliable	Not validated
	Neuropsychological tests of cognition	Not tested for reliability
	Measures of memory, attention, spatial reasoning, math reasoning, decision making, and judgment	Measures of mood, vigilance, or alertness

Exclusion criteria

The term cognition enhancement is used rather liberally in research. This review is focused on enhancement in specific areas of cognitive functioning. Therefore, studies that used only measures of alertness, vigilance, and mood were excluded from the analysis given that the focus of the review is enhancement of *cognitive performance*. Also, studies using only measures of group performance were excluded. All foreign language articles were excluded due to the lack of translation resources available to the investigators. Studies of unhealthy or abnormal populations, of humans under the age of 18 years or over the age of 50 years, or of animals were excluded. Studies using measures of cognition that have not been validated or tested for reliability were excluded.

Procedure

The analysis was carried out according to the guidelines for systematic reviews and meta-analyses provided by Littell, Corcoran, and Pillai (2008) and Lipsy and Wilson (2001).

The librarian first located potentially relevant studies using the search criteria specified above. The investigators reviewed the titles and abstracts of the search results and requested full text versions of potentially relevant articles. All full text reports were given a study number and reviewed for study eligibility (see appendix A for study eligibility form). All eligible studies were independently read and reviewed for study quality assessment by the first three authors of this report (see appendix B for study quality assessment form). The investigators collectively determined which studies met study quality standards and were to be included in the analysis. Minor discrepancies were settled through discussion and the investigators came to absolute agreement. The studies which met eligibility and quality standards were then reviewed for comparability. Data for these studies was extracted and maintained in a database for statistical analysis. The review results are displayed in table 3. The level of review to which studies were subjected is indicated in the reference section. All article databases were managed using Microsoft Excel.

Table 3.
Literature search and review results.

Search Results (January 2009)	449
Duplicated citations	147
Judged irrelevant by title and abstract	171
Full text retrieved	131
Ineligible (reviews)	11
Relevant Reports	120
Excluded due to population, design, non-cognitive outcome measures, unavailable data	91
Read for study quality	29
Excluded due to poor study quality	16
Met study quality standards	13
Excluded due to incomparable outcome measures	10
Included studies	3

After study quality was assessed and the final three articles to be included in the analysis were identified, the comparability of the dependent measures was evaluated. The three studies used a number of similar tests, including many from the same battery of tasks (e.g., Cambridge Assessment Neuropsychological Test Assessment Battery [CANTAB]). The tasks used to assess cognition in the three included studies are described below.

Cognitive measures

a. The Trail making tests (versions A and B) measure speed of visual search and mental flexibility. A participant is tasked with connecting, by making pencil lines, a series of numbers or numbers and letters, in the proper order. The dependent measure of interest was the time to complete the task and was reported in seconds.

b. The Digit Span test is a well known test of attention and working memory. Participants are asked to repeat a string of digits of increasing length from two to nine digits long. The participant is asked to repeat the string forward and backwards. The dependent measure of interest was the backward score, or the number of strings correctly repeated backwards.

c. The Logical Memory task tests a participant's recall of a story immediately and 20 minutes after hearing the story. The number of units correctly recalled is scored. The dependent measure of interest was the number of correct units recalled immediately.

d. The Stroop test is a well known test of attentional interference. Participants are presented with color words (e.g., blue, green, red) and asked to read the word as quickly as possible. However, the font color is either congruent with the word meaning or incongruent (e.g., the word "blue" printed in green font). The dependent measure of interest was the interference index, a ratio of the time required to name congruent versus incongruent words.

e. The Clock Drawing task measures visuospatial abilities as participants are asked to draw the face of a clock with the hands indicating a time of 3:40. The dependent measure of interest was the drawing score which ranged from 1 to 10 with a lower score indicating less accuracy.

f. The Controlled Oral Word Association test (COWAT) asks a participant to name as many words that begin with a specific letter or belong to a specific category as possible. The dependent measures of interest were the total number of words produced for both the letter and category task.

g. The tests included in the CANTAB battery included Rapid Visual Information Processing (RVIP), Spatial Working Memory (SWM), the Stockings of Cambridge (SOC), Intra/extra Dimensional set shift (IED), and Delayed Matching to Sample (DMTS). Detailed information regarding these tasks can be found in (CANTABeclipse, 2006).

(1) The RVIP task tests sustained visual attention in which participants must identify a consecutive sequence of numbers. The dependent measure of interest was mean latency, or the mean time taken to respond and is measured in milliseconds.

(2) The SWM task tests a participant's ability to manipulate spatial information in working memory. A participant must search for a token in any number of boxes. The dependent measure of interest was the strategy score, which measures how effectively a participant used a strategy while searching for the tokens. The higher the score, the worse the participant used the strategy.

(3) The SOC task is a test of spatial planning in which participants must move colored balls to match a given arrangement. The dependent measure of interest was the number of problems solved in the minimum moves.

(4) The IED task, is a test of mental flexibility. A participant must select the correct figure after learning rule is correct, and once it has been learned, the rules will change. The dependent measure of interest was total errors.

(5) The DMTS task is a test of visual episodic memory. The participant is required to identify a figure he/she had seen previously. The dependent measure of interest was the percentage of correctly identified figures.

Statistical analysis approach

Effect size was calculated for each study for each dependent measure using an unstandardized mean difference (standardization was not necessary since the same tasks were used across all studies). The inverse variance weight was calculated for each study and, finally, tests for overall effect and homogeneity (Q-statistic) were conducted.

Results

The results of the literature search, eligibility assessment, and study quality assessment yielded three modafinil studies for inclusion in the meta-analysis. A summary of the test population and study design characteristics for the three studies is presented in table 4. All of the included articles were published as full publications (rather than abstract format only).

Table 4.
Included Study Characteristics

Characteristics	*Randall et al., 2003*	*Randall et al., 2005*	*Turner et al., 2003*
Drug: modafinil	Y (yes)	Y	Y
Doses: 100 mg, 200mg, placebo	Y	Y	Y
Double-blind assignment	Y	Y	Y
Random Assignment	Y	Y	Y
Sample Size	30 (10 per group)	60 (20 per group)	60 (20 per group)
Age Range	20-22	29-22	20-29
Gender	19 male, 11 female	29 male, 31 female	All male
Healthy	Y	Y	Y
CANTAB Battery	Y	Y	Y
Sub-tests:			
Trail Making Test A	Y	Y	
Rapid Visual Information Processing	Y	Y	Y
Digit Span		Y	Y
Spatial Working Memory		Y	Y
Logical Memory	Y	Y	
Trail Making Test B	Y	Y	
Stockings of Cambridge	Y	Y	
Stroop	Y	Y	
Clock Drawing	Y	Y	
Controlled Oral Word Association Test	Y	Y	
Intra/extra Dimensional Set Shift	Y	Y	Y
Delayed Matching to Sample	Y		Y

Given the similarities of the studies (2 of 3 studies included were the same research team/personnel) and populations tested, as well as a non-significant Q-statistics (thus suggesting homogeneity of studies), a fixed-effects model was fit to the data. Even though only three small sample studies were included (thus few effect sizes based on relatively small samples used to compute the Q-statistics) which lends to low statistical power for rejecting homogeneity, the similarity of the studies supported the use of a fixed-effects model. Two sets of analyses were conducted: one comparing placebo to a modafinil dose of 100 milligrams and one comparing placebo to a modafinil dose of 200 mg. The statistically significant results of the first and second sets of analyses are displayed in Forest plots as figures 1 and 2, respectively. Non-significant results are included in appendices C and D.

Cognitive Test	*N*	Treatment Mean (*SD*)	*N*	Control Mean (*SD*)	Effect Size (unstandardized mean difference)	Weight	95% Confidence Interval (CI)
RVIP (mean latency (ms))							
Randall et al., 2005	20	0.95 (0.89)	20	0.9 (0.04)		25.198	
Turner et al., 2003	20	0.84 (0.48)	20	0.945 (0.07)		84.998	
Subtotal (95% CI)	40		40				[-891.658, -891.284]
Test for heterogeneity: Q(1) = 0.498, p >.05							
Test for overall effect: Z = -9358.166, p < .05							
					Favors Treatment / Favors Control		
Digit Span (backwards score)							
Randall et al., 2005	20	9.6 (2.24)	20	8.2 (2.68)		1.639	
Turner et al., 2003	20	10.7 (1.87)	20	8.65 (2.41)		2.149	
Subtotal (95% CI)	40		40				[24.382, 26.396]
Test for heterogeneity: Q(1) = 0.393, p >.05							
Test for overall effect: Z = 49.420, p < .05							
					Favors Treatment / Favors Control		
SOC (problems solved in min. moves)							
Randall et al., 2005	20	9.4 (2.24)	20	8.8 (1.79)		2.433	
Randall et al., 2003	10	9.6 (2.21)	10	9.0 (2.21)		1.024	
Subtotal (95% CI)	30		30				[6.113, 8.222]
Test for heterogeneity: Q(1) = 0.000, p >.05							
Test for overall effect: Z = 13.326, p < .05							
					Favors Treatment / Favors Control		
Clock Drawing (score)							
Randall et al., 2005	20	8.9 (1.34)	20	9.1 (0.89)		7.729	
Randall et al., 2003	10	9.4(1.26)	10	8.8 (1.58)		2.449	
Subtotal (95% CI)	30		30				[-1.394, -0.165]
Test for heterogeneity: Q(1) = 1.190, p >.05							
Test for overall effect: Z = -2.488, p < .05							
					Favors Treatment / Favors Control		

Figure 1. Forest plot displaying significant results for analysis of modafinil (100milligrams).

In the first set of analyses comparing the efficacy of a modafinil dose of 100 mg to enhance cognition to that of placebo, there was a significant overall effect for the rapid visual information processing test (RVIP; Z = -9358.17, CI = 95%, p < .05), backwards digit span test (Z = 49.42, CI = 95%, p < .05), Stockings of Cambridge task (SOC; Z = 13.33, CI = 95%, p < .05), and clock drawing test (Z = -2.49, CI = 95%, p < .05). All tests for overall effect favored treatment (100 milligrams of modafinil) over control (placebo). These cognitive tests measure sustained attention, working memory, spatial planning, and executive function.

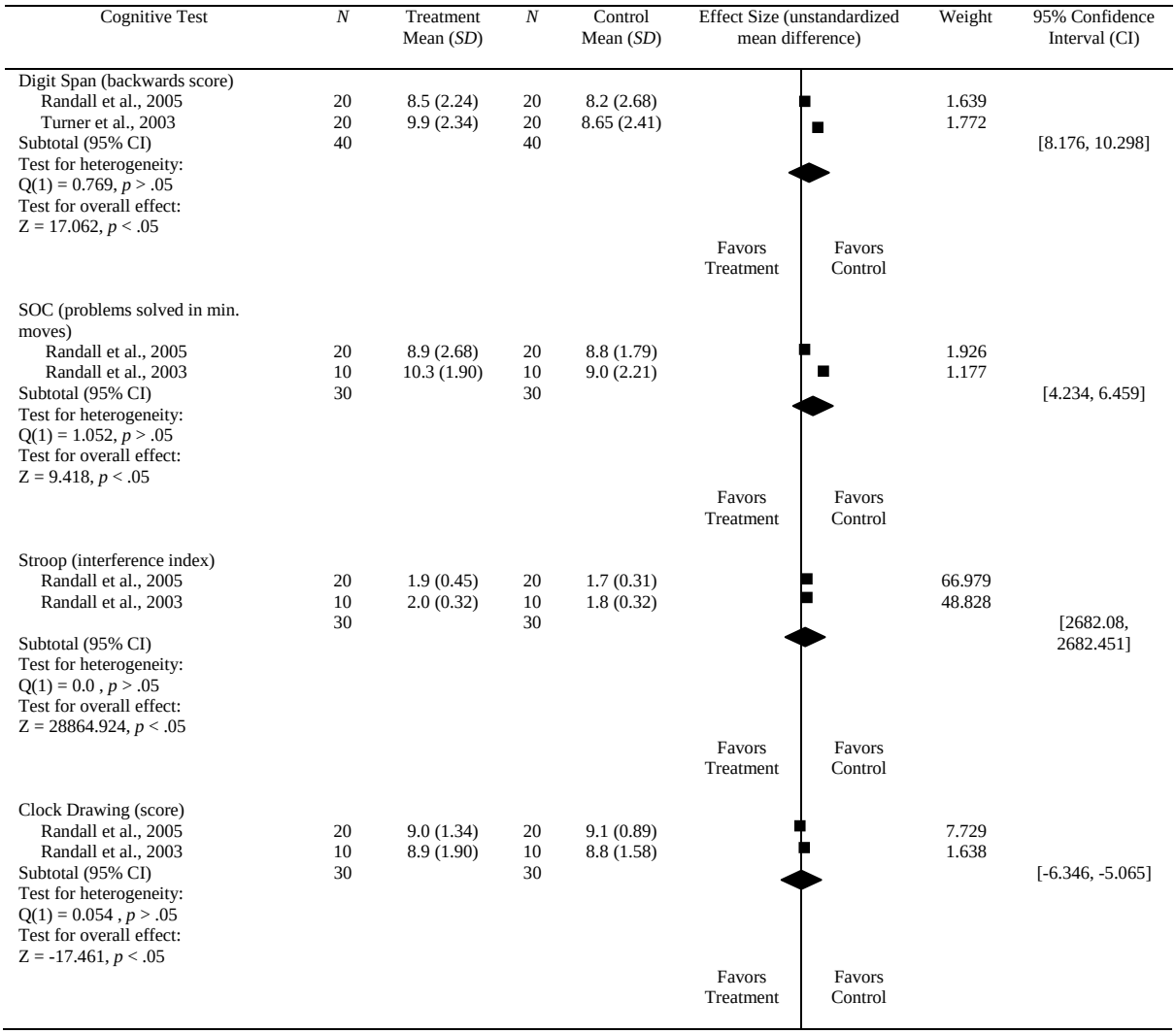

Figure 2. Forest plot displaying significant results for analysis of modafinil (200 milligrams).

In the second set of analyses comparing the efficacy of a modafinil dose of 200 mg to enhance cognition to that of placebo, there was a significant overall effect for backward digit span test (Z = 17.06, CI = 95%, $p < .05$), SOC (Z = 9.42, CI = 95%, $p < .05$), Stroop (Z = 28864.92, CI = 95%, $p < .05$), and clock drawing test (Z = -17.46, CI = 95%, $p < .05$). The test for overall effect that favored treatment (200-mg dose of modafinil) over control (placebo) was the clock drawing test. All other tests for overall effect favored control (placebo) over treatment (200-mg dose of modafinil). These cognitive tests measure working memory, attentional interference, spatial planning, and executive function. It should be noted that the Randall et al., 2003, study reported significant effects only for the 100-mg dose of modafinil (low dose) and no significant effects for the 200-mg dose of modafinil (high dose) which is inconsistent with the results reported by Randall et al. (2005) which showed significant effects of both doses.

Discussion

There were two main objectives of this study: to conduct a meta-analysis of cognition enhancement pharmaceuticals in healthy volunteers and to review the literature to identify research gaps for future study.

Objective 1: Meta-analysis of modafinil results

The results of this meta-analysis suggest that modafinil may have limited cognition enhancing properties (particularly limited to sustained attention, attentional interference, working memory, spatial planning, and executive function) in healthy young adults under normal conditions. (Note that this analysis does not have implications for cognition enhancement under conditions of operational stress.) The two studies conducted by the same research team reported slightly different results which may be attributed to the increased sample size and statistical power in the latter of the two studies. The results also suggest differences in the effectiveness of a low dose (100-mg) versus a high dose (200-mg) of modafinil such that a low dose promotes cognition to a greater extent than a high dose. This finding is most likely driven by the fact that one study employing a 200-mg dose of modafinil did not report any significant effects on cognitive performance which is inconsistent with the other two studies. Largely, modafinil research focuses on restoring performance or attenuating performance deficits under conditions of fatigue and sleep deprivation; such studies were excluded from this analysis. Under sleep deprivation conditions, modafinil is effective at maintaining an acceptable level of performance in both cognitive and aviator performance (e.g., Caldwell et al., 1999; Whitmore, Doan, Heintz, Hurtle, Kisher, and Smith, 2004). Thus, the results of this meta-analysis are consistent with these findings.

Ethical considerations

As the ultimate goal of this review is to provide interpretation of the appropriateness of cognition-enhancing pharmaceuticals in military contexts, careful consideration must be given to ethical concerns. It should be noted that although the results of this study show promise for modafinil as a cognition-enhancing agent, its use in this capacity for otherwise healthy, well-rested individuals is not approved by the Food and Drug Administration (FDA). Current indications include narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift work sleep disorder (Lexi-Comp, 2010). Medication prescription or use for an indication other than that approved by the FDA is considered “off-label.” This practice is common and legal. Whether it is safe or appropriate depends on its judicious application.

Mehlman (2010) provides a succinct summary of the legal aspects, appropriateness, and controversy concerning off-label use in his bioethics column. The FDA acknowledges that it does not regulate the practice of medicine, *per se*, and an approved drug may be prescribed by a clinician for purposes other than its explicit labeling. In a Supreme Court decision in 2001, off-label use was deemed “accepted and necessary” (Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 350, 2001), while an appellate court decision in 2000 noted that “off-label use of some drugs is frequently considered to be ‘state-of-the-art’ treatment’” or “may even define the standard of care” (Richardson v. Miller, 44 S.W.3d 1, 13, n.11, Tenn. Ct. App., 2000).

Off-label use is common. Such use may result from an inference of drug class effect, use in clinical conditions similar to or with shared pathophysiology as an indicated condition, new-found knowledge of receptor-mediated drug action, and others (Stafford, 2008). One can see examples of off-label use along the entire spectrum of care from first-line therapy algorithms to sanctioned treatment guidelines and best-practices through therapies of last resort. Using data from the National Disease and Therapeutic Index, Radley, Finkelstein, and Stafford (2006) determined that more than one in five prescriptions were for off-label indications, exceeding 50% for some classes of medications. The authors go on to caution that much off-label use has little or no scientific support. Indeed, evidence-based medicine has become the standard of care, and patients deserve therapeutics that are fully evaluated as safe and efficacious. But in many instances, sound clinical science does support the use of many off-label prescriptions, and the freedom of clinicians to exploit off-label use does carry advantages. Often, there are indications whereby the pharmaceutical companies have no incentive to develop, test, and market a drug—a lengthy and expensive process. Furthermore, off-label use permits clinicians flexibility to adapt to emerging scientific evidence and innovation where approved treatments have failed or do not exist (Stafford, 2008).

Given that off-label use is legal and common, and presupposing that it is employed judiciously whereby safety and efficacy data have been established, one may still debate the position of prescribing drugs for "enhancement," for an individual in a *non*-pathological condition. Perhaps a perspective from the discipline of aerospace medicine is appropriate whereby health promotion, disease prevention, and even treatment often entails a *normal* patient operating in a very *abnormal* environment—hypobaria, hypoxia, extremes of temperature, vibration, noise, acceleration, radiation, and others. On the contrary, traditional medicine most often addresses a patient's pathological condition in a normal environment. For the Soldier, one cannot conceive of a more abnormal environment than combat.

Russo (2007) frames the ethical considerations regarding such use citing issues of individual autonomy and choice, safety, and necessity. Caldwell (2008) acknowledges that the military's use of "cognitive performance enhancers" has often received negative attention and argument from media and scientists alike. However, he provides a logical, compelling argument for ethical application with the following provisos (adapted from Russo):

> (1) the decision to use a performance-enhancing/sustaining medication rests freely with the individual; (2) the use of the drug is safe within the context in which it is used, (3) the manner of the substance's use remains consistent with its dosage and pharmacologic function, and (4) in general, the military employs medication options only after exhausting nonpharmacologic alternatives.

In summary, the military has long facilitated (indeed, mandated) pharmaceuticals such as immunizations and prophylaxis in healthy Soldier populations where the threat is clearly identified, the risk is unacceptable, the science is sound, the drugs are safe, and the fighting force must be protected and sustained. In the case of cognitive enhancement, for example, one may characterize the threat as an intrinsic agent such as fatigue from necessary sustained combat

operations. And while its employment in this capacity may very well prevent a mishap or enable performance to complete the mission, such application does bear ethical considerations.

Military and operational considerations

The U.S. Army is regularly called upon to conduct operations in austere environments—sustained operations, sleep deprivation, physical and psychological stress, circadian asynchrony, climatic extremes, and hypobaria are all conditions under which Soldiers are regularly required to retain a high degree of functionality in order to prosecute the mission. These extreme conditions increase Soldier risk, degrade optimum duty performance, and can jeopardize mission completion.

Many aspects of combat have not changed through the years, and there is historical precedent for the use of cognitive performance enhancing agents in warfare. German, Japanese, and British forces, for example, all used amphetamines, which impact attention capabilities, (available by prescription in 1927) to enhance battlefield performance during World War II (Caldwell, 2008). Of course, many Soldiers simply self-medicate with over-the-counter agents such as caffeine, nicotine, nutritional supplements, or other agents. Self-medication can be problematic, however—it's not regulated or conducted with Command or physician oversight, it's not integrated into a comprehensive program, and it can sometimes entail substances that are potentially harmful and dangerous.

Caffeine requires no prescription and is endorsed by the U.S. Army as a pharmacological countermeasure for the maintenance of performance during sustained operations (Department of the Army, 2009). Caldwell et al. (2009) notes that caffeine is a very effective stimulant, but tolerance to cortical arousal can occur with regular use of > 200- to 300-mg per day. It is most effective when daily use is held to a minimum, and then increased (no more than 1000-mg per day) when the desired effect is necessary (so called "tactical caffeine use"). Caffeine gum (Stay Alert®) is also available through the military supply system (NSN #8925-01-530-1219) (Department of the Army, 2009).

Nicotine is a well-known and effective stimulant. Arguably, tobacco has been part of the "military culture" for many years. Lamentably, given the pernicious health effects, one in three service members currently use tobacco products (compared with the national average of one in five) costing the Department of Defense $846 million and the Department of Veterans Affairs $6 billion per year in tobacco-related illness treatment (Zoroya, 2009). Over-the-counter nutritional supplements are problematic, as well. Supplements are not regulated by the FDA (they are regulated by the 1994 Dietary Supplement Health and Education Act) (FDA, 2010). FDA review, approval, and oversight are not required—it is left to the manufacturers to ensure safety and any claims for indications and effectiveness. This has proven dubious with issues of quality and contamination, dangerous substances, unfounded claims, and other safety and oversight concerns (Fox, 2010).

It is important to note that while operational risk mitigation and Soldier performance are regular considerations for Commanders, pharmacologic agents are not first-tier solutions. In fact, they are most often employed when non-pharmacologic measures have been exhausted or are simply not feasible. Non-pharmacologic countermeasures might include operation planning

considerations and changes, circumspect duty-day schedules and work hour policies, risk assessment of the mission complexities, strategic napping, timed exercise, prudent nutrition, circadian shifting, and others.

Military aviation serves as a good example in this case. Aviation is a community that is highly regulated, extremely safety conscious, and often at the leading scientific and operational edge of the military. Using pilot fatigue as an example, all three services allow for the judicious, controlled use of alertness-promoting agents (e.g., dextroamphetamine) in pilots and aircrew when non-pharmacologic countermeasures have been exhausted. The Army policy, also representative of the other services, mandates that use must be on a short-term basis, must require operational necessity (combat or exceptional circumstances), must be under direct supervision of the flight surgeon, and must be authorized by the Commander and Chain-of-Command (Department of the Army, 2006). Furthermore, any employment of these agents must be with documented informed consent, as part of an overarching fatigue-management program, and with a safety "ground test" prior to its operation use (with medical documentation and surveillance of side effects). Currently, all three services have provisions for the use of dextroamphetamine in this capacity; while the Air Force has also authorized modafinil (approval for modafinil is expected imminently for both the Navy and Army).

Objective 2: Identified research gaps and future studies

The literature search indicated that there is limited research conducted on cognition enhancement in healthy, young adults and even less under conditions of operational stress with the exception of sleep deprivation. One drug of particular interest for cognition enhancement is methylphenidate. Despite the growing popularity of this drug in civilian populations (e.g., college students' use as a "study aid"), the efficacy of this drug in a healthy population has not been adequately studied nor has it been studied under conditions of sleep deprivation (or other operational stressors). Recently, a *60 Minutes* news special detailed the popularity of attention-enhancing medications, including methylphenidate, in civilian settings, specifically college campuses ("Popping pills," 2010). When interviewed, an undergraduate student replied that taking these pills while studying for final exams is "the norm." The special referenced a survey study at the University of Kentucky in which 34% of undergraduate students reported taking ADHD stimulants without a prescription (DeSantis, Webb, and Noar, 2008). Dr. Nora Volkow, a psychiatrist at the Brookhaven National Laboratory, cautioned against the addictive nature of these medications and that little is known about their long term effects on developing brains. Given the popularity and social acceptance of pharmaceutical cognition enhancement, it is rather alarming that this large gap in the literature exists. However, researchers are currently working to bridge this gap including Dr. Volkow who is currently studying methylphenidate in sleep-deprived participants.

Limitations

One limitation of this study is the relatively small number of studies which met the conservative inclusion criteria for the meta-analysis. The authors chose to adopt a conservative approach for two reasons: (1) to ensure the quality of the studies included in the analysis, and (2) to minimize the degree of heterogeneity between studies. There is much controversy in the

literature regarding whether a more inclusive, liberal approach or a less inclusive, conservative approach is ideal for conducting a meta-analysis. While the authors recognize that a more liberal approach would have allowed for the inclusion of more studies, the results of this analysis have implications for pharmaceutical use in military populations which is a sensitive topic that deserves and requires a high level of scrutiny. A second limitation is that the study was restricted to only some drugs/drug classes. Subsequently, potential cognition enhancing drugs/stimulants were excluded (e.g., dextroamphetamine). Therefore, this meta-analysis cannot be considered comprehensive in terms of drugs included. Finally, the authors chose to limit included research designs to between-subjects designs given that it is not advisable to combine effect sizes from both designs (within- and between- subjects).

Conclusions

That fact remains that much is asked of Soldiers—dangerous missions under very difficult circumstances and extreme environments. The use of cognitive enhancing agents in a manner that is voluntary, safe, scientifically valid, controlled, and part of a comprehensive plan does have a role. The findings of this analysis suggest that modafinil (at both low and high doses) shows promise as an enhancement agent, however, further research on its efficacy in healthy individuals under normal conditions is needed. Likewise, much research is needed on other pharmaceuticals that show promise of cognition enhancement in healthy adults under normal and operational stress conditions. Finally, a systematic review of the excluded studies from this meta-analysis would be a beneficial addition to the literature.

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Appendix A.

Study Eligibility Form.

Study Eligibility Coding Form:		
Study Number		
Title		
Author		
Year		
Source		
Language		
Study Design		
Intervention Type (Drug)		
Dose		
Population: Age		
Withdrawals		
Population: Gender		
Population: Healthy?		
Population: US?		
Population: Race		
N exp. Group		
N control group		
Name of Outcome Measure		
Reliability and validity of measure		
Objective behavioral measure?		
Construct measured		
Eligible? (Yes or No)		
Justification:		

Appendix B.

Study Quality Assessment Form.

Study quality standards

1. Random generation of allocation (assignment) to groups (explicitly stated of either computer- generated random numbers, table of random numbers, drawing lots or envelopes, coin tossing, shuffling, cards, or throwing dice)
   -Met
   -Unclear
   -Unmet

2. Allocation concealment (participants and investigators cannot foresee assignments; e.g., central randomized performed at site remote from trail location or monitored use of sequentially numbered, sealed, opaque envelopes)
   -Met
   -Unclear
   -Unmet

3. Avoidance of performance bias (no treatment differences between groups other than the main intervention contrasts)
   -Met
   -Unclear
   -Unmet

4. Avoidance of attrition bias (no treatment differences between groups other than the main intervention contrasts)
   -Met for all outcomes
   -Met for some outcome
   -Unclear
   -Unmet

5. Avoidance of detection bias (assessor unaware of the assigned treatment when collecting outcome measures)
   -Met for all outcomes
   -Met for some outcomes
   -Unclear
   -Unmet
6. Standardized observation periods (follow-up data were collected from each case at a fixed point in time after random assignment)

- Met for all outcomes
-Met for some outcomes
-Unclear
-Unmet

7. Validated outcome measures (use if instruments with demonstrated reliability and validity in the sample or similar samples OR use of public agency administrative data, behavorial, or biological measures)
   -Met for all outcomes
   -Met for some outcomes
   -Unclear
   -Unmet

8. Conflicts of interest (researchers or data collectors would benefit if results favored drug OR the control group)

   -Clear conflict of interest (explain)
   -Possible conflict of interest (explain)
   -Conflict of interest is unlikely (explain)
   -Unclear

9. Allegiance bias: Is there any indication that researchers believed that drug was better/worse than the alternatives before the study began?

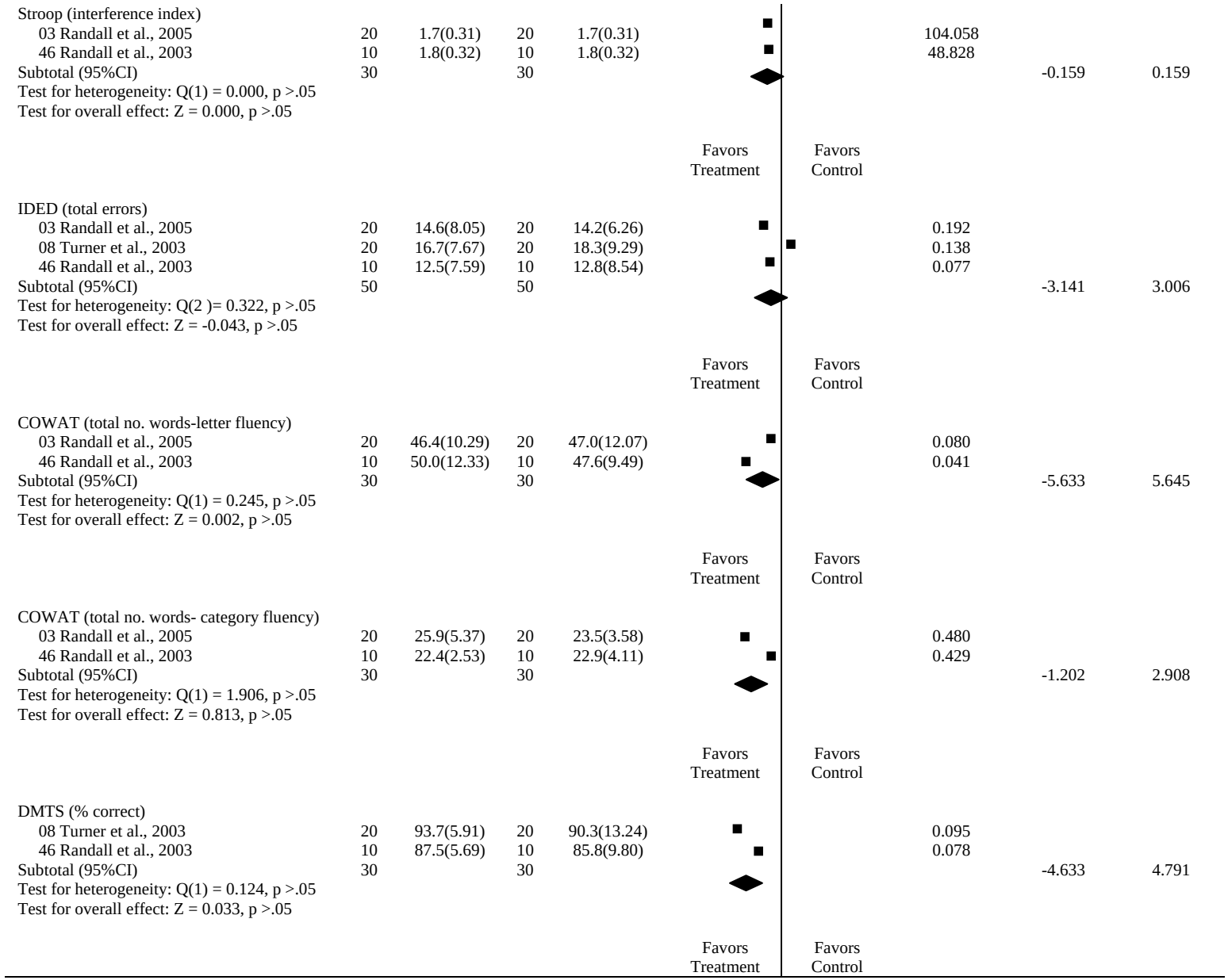
   -Yes (explain)
   -No (explain)
   -Can't tell

10. Comments:

Appendix C.

100 mg modafinil Forest plot.

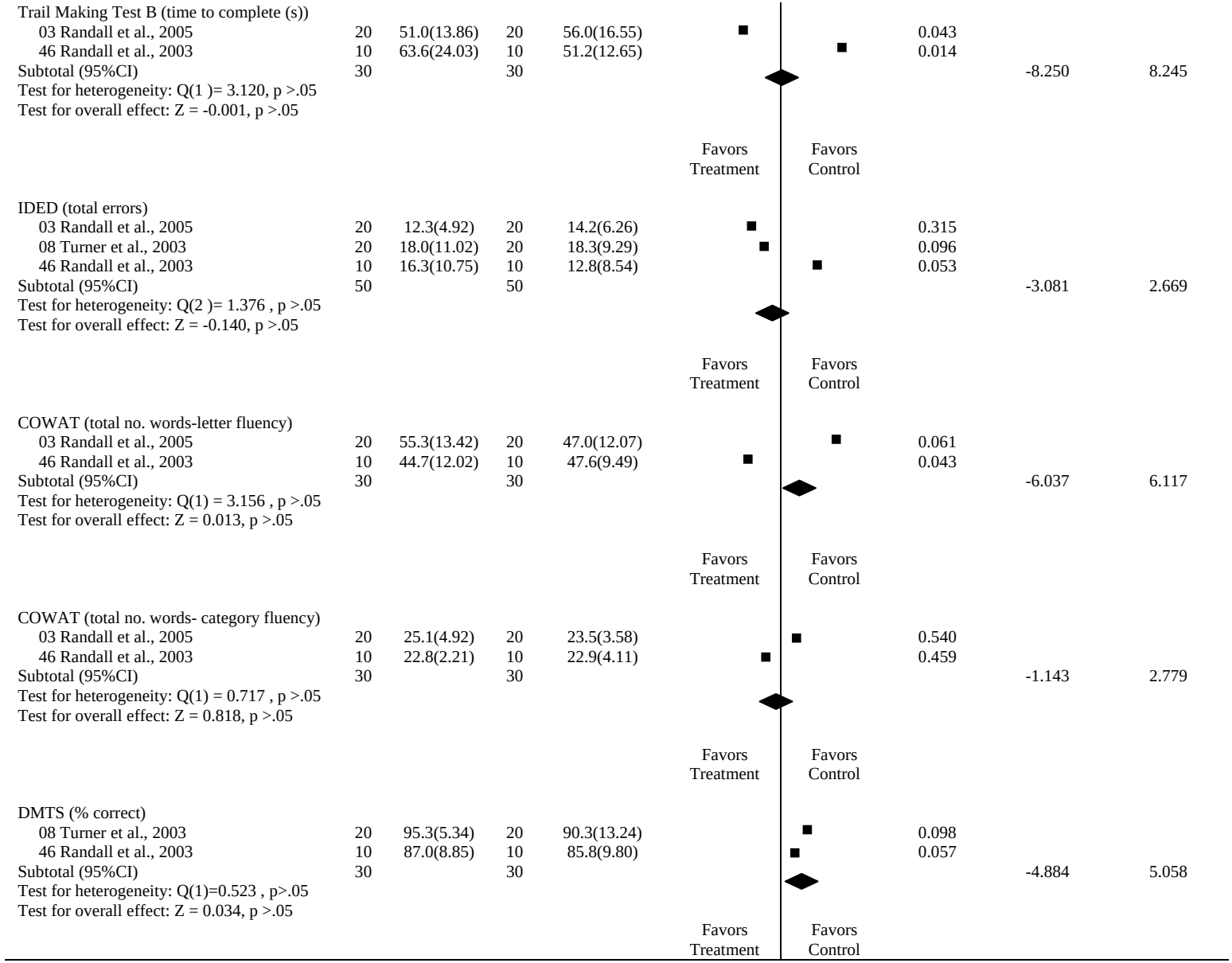
Cognitive Test	N	Treatment Mean (SD)	N	Control Mean (SD)	Effect Size (unstandardized mean difference)	Weight	-95% CI Lower bound	+ 95% CI Upper bound
Trail Making Test A (time to complete (s))								
03 Randall et al., 2005	20	21.3(5.37)	20	25.4(10.73)		0.139		
46 Randall et al., 2003	10	23.3(7.27)	10	26.3(6.96)		0.099		
Subtotal (95%CI)	30		30				-4.226	3.815
Test for heterogeneity: Q(1) = 0.070, p >.05								
Test for overall effect: Z = -0.100, p > .05								
					Favors Treatment / Favors Control			
Spatial Working Memory (strategy score)								
03 Randall et al., 2005	20	33.3(5.81)	20	30.8(5.81)		0.296		
08 Turner et al., 2003	20	26.4(5.56)	20	25.6(6.63)		0.267		
Subtotal (95%CI)	40		40				-2.074	3.149
Test for heterogeneity: Q(1) = 0.406, p >.05								
Test for overall effect: Z = 0.404, p >.05								
					Favors Treatment / Favors Control			
Logical Memory (no. units recalled-immediate)								
03 Randall et al., 2005	20	15.9(4.47)	20	14.6(4.47)		0.500		
46 Randall et al., 2003	10	16.6(5.38)	10	15.4(2.53)		0.283		
Subtotal (95%CI)	30		30				-1.439	2.990
Test for heterogeneity: Q(1) = 0.002, p >.05								
Test for overall effect: Z = 0.687, p >.05								
					Favors Treatment / Favors Control			
Trail Making Test B (time to complete (s))								
03 Randall et al., 2005	20	47.4(14.31)	20	56.0(16.55)		0.042		
46 Randall et al., 2003	10	49.9(14.86)	10	51.2(12.65)		0.026		
Subtotal (95%CI)	30		30				-7.541	7.487
Test for heterogeneity: Q(1) = 0.859, p >.05								
Test for overall effect: Z = -0.007, p >.05								
					Favors Treatment / Favors Control			


Stroop (interference index)
03 Randall et al., 2005 20 1.7(0.31) 20 1.7(0.31) 104.058
46 Randall et al., 2003 10 1.8(0.32) 10 1.8(0.32) 48.828
Subtotal (95%CI) 30 30 -0.159 0.159
Test for heterogeneity: Q(1) = 0.000, p >.05
Test for overall effect: Z = 0.000, p >.05
Favors Treatment
Favors Control
IDED (total errors)
03 Randall et al., 2005 20 14.6(8.05) 20 14.2(6.26) 0.192
08 Turner et al., 2003 20 16.7(7.67) 20 18.3(9.29) 0.138
46 Randall et al., 2003 10 12.5(7.59) 10 12.8(8.54) 0.077
Subtotal (95%CI) 50 50 -3.141 3.006
Test for heterogeneity: Q(2)= 0.322, p >.05
Test for overall effect: Z = -0.043, p >.05
Favors Treatment
Favors Control
COWAT (total no. words-letter fluency)
03 Randall et al., 2005 20 46.4(10.29) 20 47.0(12.07) 0.080
46 Randall et al., 2003 10 50.0(12.33) 10 47.6(9.49) 0.041
Subtotal (95%CI) 30 30 -5.633 5.645
Test for heterogeneity: Q(1) = 0.245, p >.05
Test for overall effect: Z = 0.002, p >.05
Favors Treatment
Favors Control
COWAT (total no. words- category fluency)
03 Randall et al., 2005 20 25.9(5.37) 20 23.5(3.58) 0.480
46 Randall et al., 2003 10 22.4(2.53) 10 22.9(4.11) 0.429
Subtotal (95%CI) 30 30 -1.202 2.908
Test for heterogeneity: Q(1) = 1.906, p >.05
Test for overall effect: Z = 0.813, p >.05
Favors Treatment
Favors Control
DMTS (% correct)
08 Turner et al., 2003 20 93.7(5.91) 20 90.3(13.24) 0.095
46 Randall et al., 2003 10 87.5(5.69) 10 85.8(9.80) 0.078
Subtotal (95%CI) 30 30 -4.633 4.791
Test for heterogeneity: Q(1) = 0.124, p >.05
Test for overall effect: Z = 0.033, p >.05
Favors Treatment
Favors Control

Appendix D.

200 mg modafinil Forest plot.

Cognitive Test	N	Treatment Mean (SD)	N	Control Mean (SD)	Effect Size (unstandardized mean difference)	Weight	-95% CI Lower bound	+95% CI Upper bound
Trail Making Test A (time to complete (s))								
03 Randall et al., 2005	20	24.1(6.26)	20	25.4(10.73)		0.130		
46 Randall et al., 2003	10	28.1(13.91)	10	26.3(6.96)		0.041		
Subtotal (95%CI)	30		30				-4.757	4.725
Test for heterogeneity: Q(1) = 0.301 , p >.05								
Test for overall effect: Z = -0.007, p >.05								
					Favors Treatment / Favors Control			
RVIP (mean latency (ms))								
03 Randall et al., 2005	20	0.95(0.04)	20	0.9(0.04)		6250.000		
08 Turner et al., 2003	20	0.959(0.06)	20	0.945(0.07)		2352.941		
46 Randall et al., 2003	10	0.8(0.63)	10	1(0)		25.195		
Subtotal (95%CI)	50						2855829.957	2855830.000
Test for heterogeneity: Q(2) = 4.171, p >.05								
Test for overall effect: Z = 2.653E+8, p >.05								
					Favors Treatment / Favors Control			
Spatial Working Memory (strategy score)								
03 Randall et al., 2005	20	31.5(6.71)	20	30.8(5.81)		0.254		
08 Turner et al., 2003	20	26.6(5.59)	20	25.6(6.63)		0.266		
Subtotal (95%CI)	40		40				-2.488	2.949
Test for heterogeneity: Q(1) = 0.012, p >.05								
Test for overall effect: Z = 0.166, p >.05								
					Favors Treatment / Favors Control			
Logical Memory (no. units recalled-immediate)								
03 Randall et al., 2005	20	16.0(4.47)	20	14.6(4.47)		0.500		
46 Randall et al., 2003	10	16.5(2.85)	10	15.4(2.53)		0.689		
Subtotal (95%CI)	30		30				-0.064	3.531
Test for heterogeneity: Q(1) = 0.026, p >.05								
Test for overall effect: Z = 1.890, p >.05								
					Favors Treatment / Favors Control			


Trail Making Test B (time to complete (s))
03 Randall et al., 2005 20 51.0(13.86) 20 56.0(16.55) 0.043
46 Randall et al., 2003 10 63.6(24.03) 10 51.2(12.65) 0.014
Subtotal (95%CI) 30 30 -8.250 8.245
Test for heterogeneity: Q(1)= 3.120, p >.05
Test for overall effect: Z = -0.001, p >.05
Favors Treatment
Favors Control
IDED (total errors)
03 Randall et al., 2005 20 12.3(4.92) 20 14.2(6.26) 0.315
08 Turner et al., 2003 20 18.0(11.02) 20 18.3(9.29) 0.096
46 Randall et al., 2003 10 16.3(10.75) 10 12.8(8.54) 0.053
Subtotal (95%CI) 50 50 -3.081 2.669
Test for heterogeneity: Q(2)= 1.376 , p >.05
Test for overall effect: Z = -0.140, p >.05
Favors Treatment
Favors Control
COWAT (total no. words-letter fluency)
03 Randall et al., 2005 20 55.3(13.42) 20 47.0(12.07) 0.061
46 Randall et al., 2003 10 44.7(12.02) 10 47.6(9.49) 0.043
Subtotal (95%CI) 30 30 -6.037 6.117
Test for heterogeneity: Q(1) = 3.156 , p >.05
Test for overall effect: Z = 0.013, p >.05
Favors Treatment
Favors Control
COWAT (total no. words- category fluency)
03 Randall et al., 2005 20 25.1(4.92) 20 23.5(3.58) 0.540
46 Randall et al., 2003 10 22.8(2.21) 10 22.9(4.11) 0.459
Subtotal (95%CI) 30 30 -1.143 2.779
Test for heterogeneity: Q(1) = 0.717 , p >.05
Test for overall effect: Z = 0.818, p >.05
Favors Treatment
Favors Control
DMTS (% correct)
08 Turner et al., 2003 20 95.3(5.34) 20 90.3(13.24) 0.098
46 Randall et al., 2003 10 87.0(8.85) 10 85.8(9.80) 0.057
Subtotal (95%CI) 30 30 -4.884 5.058
Test for heterogeneity: Q(1)=0.523 , p>.05
Test for overall effect: Z = 0.034, p >.05
Favors Treatment
Favors Control

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